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Stem Cell Transplantation in Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) remains incurable with standard therapy. Most patients with CLL have an indolent clinical course, but it is possible to identify patients with high-risk disease. Younger patients with adverse risk factors will die from their disease, and are therefore candidates for clinical trials exploring hematopoietic stem cell transplantation (HSCT). Autologous SCT is feasible and has low treatment-related mortality (TRM); but it is not curative. Myeloablative allogeneic SCT is associated with high treatment-related mortality and, TRM few late relapses, but is applicable to only a small number of CLL patients. The major focus of SCT in CLL has been with reduced-intensity conditioning (RIC) allogeneic SCT, which is applicable to the more elderly patient population with this disease and which attempts to exploit the graft-versus-leukemia (GVL) effect that exists in CLL. Steps to further decrease the morbidity and mortality of the RIC SCT, and, in particular, to reduce the incidence of extensive chronic graft-versus-host disease (cGVHD) remain the major focus. Many potential treatments are available for CLL, and appropriate patient selection and the timing of SCT remain controversial and the focus of ongoing clinical trials. The use of SCT must always be weighed against the risk of the underlying disease, particularly in a setting where improvements in treatment are leading to improved outcome.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is not a suitable treatment option for most patients with chronic lymphocytic leukemia (CLL). The disease usually follows an indolent course; many patients never require any therapy, and most patients are too elderly to undergo this procedure. High-risk patients can be identified using a number of clinical and biologic features, and such younger patients are suitable candidates for enrollment in clinical trials evaluating the role of HSCT in CLL. The role of HSCT in a number of other hematologic malignancies has been established in prospective studies, but no studies in CLL have compared the outcome after standard chemotherapy with either autologous or allogeneic HSCT. Using clinical and biologic features, it is possible to identify patients who are suitable candidates for enrollment in clinical trials evaluating the role of HSCT in CLL. The biggest challenges remain the decision of which patients are eligible for consideration of HSCT and when in their disease course HSCT should be offered.

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Patient Selection for Stem Cell Transplantation

CLL is an extremely heterogeneous disease, with the clinical course varying from patients who never require therapy to a rapidly progressive and fatal malignancy in others. Treatment guidelines state that therapy should be reserved for those with advanced, symptomatic, or progressive disease [1]. There has been significant improvement over the past decade in the results of treatment of CLL with the use of combination chemotherapy and chemoimmunotherapy [2-6] (Table 1). The results of the German CLL Study Group CLL8 study, which demonstrated higher response rates and significant improvement in progression-free survival (PFS) in patients who were treated with rituximab in combination with fludarabine (Flu) and cyclophosphamide (Cy), were presented at the recent meeting of American Society of Hematology in December 2008. In parallel with improvements in treatment outcome, there has been dramatic progress in the understanding of CLL pathophysiology, which has expanded the number of useful prognostic biomarkers including cytogenetics [7], immunoglobulin heavy chain (IgV_H) gene mutational status [8],

Table 1. Progress in the Treatment of CLL

Study	Treatment	n	CR%	OR%	PFS(months)	Reference
CALGB	Chlorambucil	181	4	37	14	Rai et al. [2]
9011	Fludarabine	170	20	63	20	
GCLLSG	Fludarabine	180	7	83	20	Eichhorst et al. [3]
CLL4	Fludarabine/Cyclophosphamide	182	24	94	48	
ECOG	Fludarabine	137	5	59	19	
E2997	Fludarabine/Cyclophosphamide	141	23	74	32	Flinn et al. [4]
LRF	Chlorambucil	366	7	72	20	Catovsky et al. [5]
CLL4	Fludarabine	181	15	80	23	
	Fludarabine/Cyclophosphamide	182	38	92	43	
MDACC Phase II	Rituximab/Fludarabine/Cyclophosphamide	224	72	95	80	Tam et al. [6]
GCLLSG	Fludarabine/Cyclophosphamide	817	?	?	Significantly prolonged	Hallek et al.
CLL8	(FC)		?	?	inRFC arm	(unpublished observation)
	Rituximab/Fludarabine/Cyclophosphamide (RFC)	patients recruited to both arms				

CR indicates complete response; OR, overall response; PFS, progression-free survival; CALGB, Cancer and Leukemia Group B; GCLLSG, German CLL study group; ECOG, Eastern Cooperative Oncology Group; LRF, Leukemia Research Fund; MDACC, M.D. Anderson Cancer Center.

zeta-associated protein 70 (ZAP70) expression [9], and CD38 expression [10] (Table 2). There is strong evidence linking prognosis with biologic markers, but it is not clear how we should use these factors in CLL management.

Attempts have been made to determine which of the risk factors in this disease are associated with sufficiently poor prognosis to merit HSCT. All phase II studies have enrolled younger patients with "high-risk" disease; this term is rather loosely defined, and it is difficult to determine precisely the risk factors used in each of the reported studies. European Bone Marrow Transplant (EBMT) guidelines have now been established outlining indications for HSCT in CLL [11]. The guidelines conclude that there is evidence base for the efficacy of allogeneic HSCT in CLL, and that this procedure is indicated in high-risk CLL patents. High-risk patients are defined in Table 3, and include those requiring treatment who have p53 abnormalities (who merit allogeneic HSCT in first response), patients who fail to achieve complete remission (CR) or who progress within 12 months after purine analogues, those who relapse within 24 months after having achieved a response with purine-analogue-based combination therapy, those who have relapsed after prior autologous HSCT, or those patients who are Flu refractory. It should be noted that none of these categories requires assessment of biologic risk factors except for cytogenetics for detection of p53 deletions. Ongoing prospective clinical studies will determine the impact of biomarkers, including IgV_H mutational status and other cytogenetic abnormalities, in identification of patients at sufficiently high risk to merit use of allogeneic HSCT in first CR (CR1).

Table 2. Impact of Molecular Markers on Prognosis in CLL

Marker		Frequency (%)	TTT (months)	OS (months)	Reference
Cytogenetics	del 13p	55	92	133	Dohner et al.
	normal	18	49	111	2000 [7]
	Trisomy 12	16	33	114	
	del 11q	13	13		
	del 17p	9	9		
IgVH	Mutated	47	110	300	Rassenti et al.
	Unmutated	53	42	115	2004 [9]
ZAP70	Negative	54	110	NS	Rassenti et al.
	Positive	46	35	NS	2004 [9]
CD38	Negative	67	94	193	Rassenti et al.
	Positive	33	40	109	2008 [10]

CLL indicates chronic lymphocytic leukemia; OS, overall survival; TTT, time to treatment.

Autologous HSCT

No studies have prospectively compared the role of standard chemotherapy with autologous HSCT in CLL, and there is no established role for this approach except in the setting of a clinical trial. A retrospective matched-pair analysis suggested a survival advantage for autologous HSCT over conventional therapy [12]. This used a risk-matched comparison between 66 patients who had undergone a uniform high-dose therapy and autologous HSCT with a database of 291 patients treated conventionally. Matched data included age, Binet stage, IgV_H mutational status, and lymphocyte count, and 44 patient pairs matched all 4 variables. With an overall median follow-up time of 70 and 86 months, survival was significantly longer for the patients who had undergone autologous HSCT compared with conventionally treated patients when calculated from diagnosis ($P = .03$) or from study entry ($P = .006$).

Table 3. EBMT Guidelines for Transplantation in CLL [11]

Allo-HSCT is a reasonable treatment option in poor-risk CLL including:
Fludarabine resistance—nonresponse or early relapse (<12 months) after purine analogue-based therapy
Relapse <24 months after purine analogue combinations or auto-SCT (+ high-risk genetics)
p53 mutation with treatment indication
Auto-HSCT indicated in clinical trial only.

CLL indicates chronic lymphocytic leukemia; HSCT, hematopoietic stem cell transplantation.

A number of phase II studies have reported outcome following autologous HSCT for CLL [13-15]. These studies have demonstrated that this approach is feasible in CLL with a treatment-related mortality (TRM) of 1% to 10%, with most toxicity occurring late. Among 115 previously untreated CLL patients prospectively enrolled in a pilot study to assess the feasibility of performing autologous HSCT only, 65 (56%) proceeded to transplant (14). Only 1 TRM was seen and the CR rate after transplantation was 74% (48 of 65). The 5-year estimated overall survival (OS) was 77.5% and PFS was 51.5%. None of the variables examined at study entry were predictive for OS or PFS, but detectable minimal residual disease (MRD) was highly predictive of disease recurrence. Of concern, 5 of 65 (8%) patients developed posttransplant acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS), a complication also seen in other series [13]. In a single-center study, among 137 patients who underwent autologous transplantation, the 1-year TRM was 4%, but rose to 10% when late events were taken into account. At the median follow-up time of 6.5 years, OS was 58% after autologous HSCT. There was no TRM among 72 patients autografted in 5 Finnish centers with median age 57 (range: 38-69) years and median of 32 (range: 6-181) months from diagnosis [15]. At median follow-up of 28 months, 37% had progressed, with median OS of 95 months and PFS 48 months.

Monoclonal antibodies (mAbs) have been used to increase the likelihood of elimination of MRD after autologous HSCT, ex vivo [13], or by in vivo treatment with alemtuzumab or rituximab. Alemtuzumab was used in the conditioning regimen for autologous HSCT in 1 arm of the German CLL Study Group CLL3 trial, and 12 of 16 patients (87%) developed a skin rash between 43 and 601 days post-SCT. In 7 patients biopsy confirmed graft-versus-host disease (GVHD) persisted for a median duration was 517 (range: 60-867) days [16]. The trial was discontinued because of the TRM, but addition of alemtuzumab led to improved disease control. When alemtuzumab was used at modified dose (10 mg subcutaneously 3 times per week for 6 weeks) in 34 patients who had had a clinical response to a Flu-based regimen, the CR rate improved from 35% to 79.5% with 56% achieving eradication of MRD [17]. Peripheral blood stem cell (PBSC) collection was subsequently successfully performed in 92%. Eighteen patients underwent auto-HSCT, with 17 remaining in CR at a median follow-up of 14.5 months post-SCT.

Most studies reported have relatively short follow-up, and therefore focus only on TRM early postransplant, but late consequences, particularly development of secondary MDS/AML, are of concern. Among 65 previously untreated patients who were treated with Flu followed by autologous HSCT, 8 developed MDS/AML [14], with a 5-year actuarial risk of 12% developing MDS/AML after autologous HSCT. Long-term follow-up reports also a high incidence of other solid tumors in 31 (19%) patients [13]. The use of total body irradiation (TBI) containing regimens appears associated with increased risk of MDS/AML.

Myeloablative Allogeneic HSCT

The major advantage of the allogeneic hSCT is the potential for a graft-versus-leukemia (GVL) effect. Evidence for a GVL effect in CLL include (1) decreased risk of relapse in patients with chronic GVHD (cGVHD), (2) increased risk of relapse with T cell depletion, and (3) clinical responses to removal of immune suppression and to donor lymphocyte infusion (DLI) [13]. Allogeneic SCT has significant morbidity and mortality, from regimen-related toxicity, GVHD, and infection, but surviving patients have long-term disease control [13,18-20]. In registry data, TRM following allogeneic HSCT in CLL patients was 46%, with mortality from GVHD of 20% [18]. Of 25 patients with CLL who underwent allogeneic hSCT at the Fred Hutchinson Cancer Center grades ii-iv acute GVHD (aGVHD) was seen in 14 patients and 10 developed clinical extensive cGVHD and estimated OS at 5 years was 32% [20]. Nonrelapse mortality (NRM) at day 100 was unacceptably high at 57% for patients conditioned with busulfan (Bu) and cyclophosphamide (Cy) compared to 17% for patients conditioned with TBI-containing regimens. Among 30 patients (20 related donors and 10 unrelated donors) transplanted for CLL between 1989 and 2001 in Vancouver with a median follow-up of 4.3 years, 47% were alive in CR, both estimated OS and disease-free survival (DFS) at 5 years were 39%. A strong GVL effect was noted with those developing aGVHD or cGVHD having near complete protection from relapse.

There are no randomized studies comparing the outcome of autologous versus allogeneic HSCT. Studies from M.D. Anderson Cancer Center demonstrate improved outcome after allogeneic compared to autologous HSCT [21], suggesting that allogeneic HSCT can induce durable remission even in patients with refractory disease. At the Dana-Farber Cancer Institute, 162 patients with high-risk CLL were enrolled in a "biologic randomization" in which 25 patients with an HLA matched sibling donor underwent T cell-depleted myeloablative allogeneic HSCT, whereas 137 with no HLA matched sibling donor underwent B cell purged autologous HSCT, with both groups receiving identical conditioning regimen using high-dose Cy and TBI [13]. The 100-day TRM was 4% after autologous or allogeneic HSCT, but later TRM had a major impact on outcome. At the median follow-up of 6.5 years, PFS was significantly longer following

autologous than T cell-depleted allogeneic HSCT, but no significant differences were observed in disease recurrence or deaths without recurrence by type of transplant. There was no difference in OS between the 2 groups, and at the median follow-up time of 6.5 years OS was 58% after autologous and 55% after allogeneic HSCT.

Reduced-Intensity Conditioning (RIC) HSCT for CLL

A major advance in reducing the short-term morbidity and mortality of allogeneic HSCT has been the introduction of nonmyeloablative or RIC regimens to allow engraftment of allogeneic stem cells. Most patients to date have been treated on experimental treatment protocols that allowed enrollment of many patients with chemorefractory end-stage disease.

RIC regimens allow transplantation in older patients, making this approach more applicable to increased numbers of CLL patients and results from the larger reported studies are shown in Table 4 [22-27]. Most patients were heavily pretreated and refractory to therapy, but despite these issues, the majority demonstrated donor engraftment, and there was a high CR rate. The ability of such approaches to eradicate MRD in patients with advanced CLL [28] and the observation of late remissions in patients treated with low doses of chemotherapy provide the strongest direct evidence for a powerful GVL in CLL. The outcome from the Fred Hutchinson Cancer Research Center multi-institutional protocol after RIC allogeneic HSCT was recently updated for 82 patients with advanced Flu refractory CLL using related (n = 52) or unrelated donors (n = 30) median age of 56 years (range: 42-72) years [22]. TRM was 23% at 5 years, with significant GVHD remaining a problem. Five-year OS was 50% and DFS was 39%. Although complications were higher in the patients with unrelated donors, there were higher CR and lower relapse rates, suggesting more effective GVL activity with unrelated donors. Forty-six patients underwent RIC transplantation at the Dana Farber Cancer Institute, 67% using unrelated donors [24]. Factors associated with increased risk of relapse include low levels of donor chimerism at day 30, chemorefractory disease, increased number of previous therapies, and adverse cytogenetics [24].

No formal assessment of RIC compared to myeloablative allogeneic HSCT has been undertaken, but the outcome after RIC allogeneic SCT of 73 patients who had undergone RIC was compared with that of 82 matched patients who had undergone standard myeloablative conditioning for CLL from the EBMT registry database during the same time period. Patients undergoing RIC transplants had significantly reduced TRM, but higher relapse incidence, and there was no significant difference in OS or PFS between these 2 groups [29]. Of particular interest is the group fo CLL patients with deletion of 17p and loss of p53. A recent report from EBMT of 44 such patients suggests that allogeneic HSCT has the potential to induce long-term remission in these very high-risk patients [30].

Addition of mAb to RIC SCT

GVHD remains the major concern after RIC HSCT, and attempts have been made to utilize mAb to reduce the incidence of GVHD without increasing the subsequent risk fo relapse. Excellent results have been obtained using RIC based on a combination of Flu and Cy with the addition of rituximab at the M.D. Anderson Cancer Center, an approach designed to maximize GVL by early tapering of immune suppression with use of rituximab and DLI. Among 39 patients treated, median age was 57 (range: 34–70) years, median time from diagnosis to transplantation was 4.5 years [26]. All patients had recurrent advanced disease, were heavily pretreated with a median of 3 (range: 2-8) chemotherapy regimens and all had been previously treated with fludarabine-rituximab-based regimens.

Table 4. RIC allogeneic SCT for CLL

n	Age (Years) (range)	Prior Regimens (range)	Chemo-refractory (%)	Prior Auto-SCT	Donor (Includes Mismatch)	TRM	GVHD (Acute) gd 2-4	(Chronic) extensive	Survival	Reference
82	82 (42-72)	4	87%	4	63% related 37% unrelated	25% overall	55%	49% related 53% unrelated	OS 50% 5 years PFS 45%	Sorror et al. 2008 [22]
77	54 (30-66)	3 (0-8)	33%	10	81% related	18% 12m	34%	58%	OS 72% 2 years PFS 56%	Dreger et al. 2003 [23]
46	53 (35-67)	5 (1-10)	57%	10	33% related 67% unrelated	17% overall	34%	43%	OS 54% 2 years PFS 34%	Brown et al. 2006 [24]
41	54 (37-67)	3 (1-8)	27%	11	58% related 42% unrelated	5% at 100 d 26% overall	10% (gd 3-4)	33%* *after DLI	OS 51 2 years PFS 45%	Delgado et al. 2006 [25]
39	57 (34-70)	3 (2-8)	Not stated		90% related 10% unrelated	2% at 100 days	45%	58%	OS 48% 4 years PFS 44%	Khouri et al. 2006 [26]
30	50 (12-63)	3 (0-8)	47%		50% related 50% unrelated	13% overall	56%	21%	OS 72% 2 years PFS 67%	Schetelig et al. 2003 [27]

DLI indicates donor lymphocyte infusion, HSCT, hematopoietic stem cell transplantation; CLL, chronic lymphocytic leukemia; OS, overall survival, PFS, progression-free survival.

At transplant, 34 patients (87%) had active disease, including 9 (23%) with evidence of Richter's transformation. In this series only 4 of the donors were unrelated. Fourteen patients required immunomodulation with rituximab and DLI for persistent disease after HSCT. Only 1 patient died early and among the 38 evaluable patients, 27 (71%) achieved CR, with estimated OS at 4 years was 48% with current PFS was 44%. Grade II-IV acute GVHD (aGVHD) was observed in 45%, but extensive chronic GVHD (cGVHD) was reduced without concomitant increased risk of relapse.

GVHD can also be decreased using alemtuzumab in the conditioning regimen, but this delays post-HSCT immune reconstitution, increases the risk of infective complications, and does appear to impair GVL. In 41 consecutive CLL patients treated (24 HLA-matched sibling donors and 17 unrelated volunteer donors, including 4 mismatched) the conditioning regimen alemtuzumab with Flu and melphalan (Mel) had significant antitumor effects, with 100% of patients with chemosensitive disease and 86% with chemorefractory disease responding [25]. The TRM rate was 26%, OS 51%, and relapse risk 29% at 2 years. GVHD rates were relatively low, with aGVHD occurring in 17 (41%) and cGVHD in 13 (33%). The unexpectedly high TRM rate was because of a high incidence of fungal and viral infections.

CONCLUSIONS

HSCT has a role to play in selected CLL patients, with major focus on the use of RIC allogeneic HSCT. Although RIC HSCT appears to result in high response rates and eradication of PCR detectable MRD, the follow-up of most clinical trials is too short to assess whether HSCT can cure CLL. Future approaches to the management of this disease must take into account the balance between the increased morbidity and mortality of HSCT in CLL with the curative potential that these approaches potentially offer, in the setting of the improvements in outcome that can now be seen using chemoimmunotherapy. In the absence of any other treatment modalities currently capable of improving outcome in this disease, HSCT should be considered as a treatment approach for younger patients with high-risk CLL early in the course of the disease, ideally in the setting of well-designed clinical trials assessing the impact of this treatment on outcome in these patients. Such trials are currently in development and will open shortly.

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